REMARKS

Upon entry of this amendment, claims 1-6, 9, 10, 12, 14 and 45-53 are pending in the instant application. In this response, claims 1, 4-6, 9, 10, 12 and 14 have been amended and claims 45-53 have been added. The claims, as amended and added herein, are fully supported by the instant specification. Accordingly, no new matter has been added. Applicants have herein cancelled claims 7, 8, 11, 13, and 15-18 without prejudice or disclaimer.

PRIORITY

The Examiner has objected to the priority claim as being improperly phrased. Applicants have amended the priority claim as suggested by the Examiner. Applicants believe that this amendment overcomes the objection and request that this objection be withdrawn.

DRAWINGS

Applicants acknowledge the Draftsperson's objection to the Drawings filed in the specification. Applicants will provide formal drawings upon determination of allowable subject matter in the present application.

SPECIFICATION

The Examiner has objected to the specification for containing an embedded hyperlink and/or other form of browser-executable code. Applicants have amended the specification to remove embedded hyperlinks and therefore respectfully request withdrawal of the objection.

CLAIM OBJECTIONS

The Examiner has objected to claims 5-6 as being substantially duplicate of claim 4 under 37 CFR 1.75. Applicants have amended claims 5-6; as such, claims 5-6 do not duplicate claim 4. Applicants believe that this amendment overcomes the objection and request that the objection be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 101

Claims 1-18 have been rejected under 35 U.S.C. § 101 for allegedly not being supported by either a specific, substantial, and credible utility or, in the alternative, a well-established utility. Applicants traverse.

The rejection is moot with respect to claims 7, 8, 11, 13, and 15-18, which have been cancelled. The rejection will be addressed as it relates to amended claims 1, 4-6, 9, 10, 12 and 14 and to new claims 45-53.

It is the Examiner's position that the asserted specific utilities for the claimed invention are not considered to be substantial or credible utilities because the utilities are generally applicable to broad classes of this subject matter (Office Action at page 5). The Examiner further states that the polymorphic nucleic acid of SEQ ID NO: 509 would not be useful for forensic identification and paternity testing (Office Action at pages 5 and 6) or for a method of treatment (Office Action at pages 6).

Pending claims 1-6, 9, 10, 12, 14 and 45-53 are directed to nucleic acids comprising the polymorphic nucleotide sequence of SEQ ID NO: 509 or a complement thereof. Specifically, the specification discloses that the nucleotide sequence of SEQ ID NO: 509 is homologous to, and a conserved nucleic acid sequence of, members of the keratinocyte growth factor protein family and is a conserved nucleic acid sequence shared by these family members as shown by BLAST analysis (*See* specification, Table 1, column 11) and asserts a utility based, in part, on homology analysis.

The Utility Examination Guidelines state that "when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the Examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." (Fed. Reg., Vol. 66. No. 4, January 5, 2001, p. 1096). If the Examiner has sufficient evidence to rebut such an assertion, and rejects the claims for lack of

utility, then the burden shifts back to the Applicant to provide evidence supporting such a well-established utility.

Nucleic acid and amino acid homology is commonly determined by the skilled artisan using BLAST (*e.g.* BLASTX, BLASTN, BLASTP, etc.) analysis or homology alignment algorithms as described in the specification (*See* specification, pg 26, lines 5-13; pg 36, line 23 – pg 37, line 6). Here, the nucleotide sequence of SEQ ID NO: 509 comprising the disclosed polymorphisms is highly homologous to, and a conserved nucleic acid sequence of, members of the keratinocyte growth factor protein family, as determined by BLASTN analysis including, but not limited to, gi|14785212|ref|XM_017651.2|.

Members of the keratinocyte growth factor protein family are known to those skilled in the art to be localized to chromosome 9q (*e.g.* Genome BLAST) and several disorders are known to be attributed to the q locus on chromosome 9 including, but not limited to, autosomal recessive ataxic cerebral palsy and hypomagnesemia with secondary hypocalcemia, as determined by OMIM Morbid Map analysis.

Accordingly, one skilled in the art would recognize that the disclosed polymorphic nucleotide sequence of SEQ ID NO: 509 of the present invention, which is highly homologous to, and a conserved nucleic acid sequence of, members of the keratinocyte growth factor protein family, and thus can be expected to function as a member of the keratinocyte growth factor protein family. As such, diseases and conditions involving altered or aberrant function of members of the keratinocyte growth factor protein family, readily identifiable by the skilled artisan, could be analyzed using the nucleotide sequence of SEQ ID NO: 509 comprising the disclosed polymorphisms of the present invention and thus these nucleic acids have an art-recognized specific, substantial, and credible utility.

In addition to the substantial utility in the field of diagnostics and specific disease markers discussed *supra*, SNPs are critical to the field of forensic medicine. The elected polymorphic nucleotide sequences of the present invention (SEQ ID NO: 509) can be amplified and utilized in forensic genotyping, the results of which can be accurate and quantifiable. Thus the specific SEQ ID NO: 509 of the present invention can be used to identify individuals who are differentiated by the disclosed polymorphism. Forensic data generated by the polymorphic nucleotide sequences of the SEQ ID NO: 509, has utility beyond human identification. It can also

be used to reconstruct the past migration history of modern humans who possess the disclosed polymorphism.

The specific polymorphic nucleotide sequences of SEQ ID NO: 509 can also be utilized in paternity testing to separate and identify individuals who have said polymorphism and in the fields of pharmacogenomics and drug development to treat diseases or conditions which may be attributable to the polymorphism disclosed in the specification.

The Utility Examination Guidelines further state that "when a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein." (Fed. Reg., Vol. 66. No. 4, January 5, 2001, p. 1096). Members of the above defined protein families share a specific, substantial, and credible utility. Moreover, the sequences of such members are sufficiently conserved, thereby imputing the same utility to a novel member of their protein class, such as the claimed nucleic acids comprising the disclosed polymorphisms of SEQ ID NO: 509.

The foregoing demonstrates that the nucleotide sequence of SEQ ID NO: 509 comprising the disclosed polymorphisms of the invention have a specific and substantial or well-established utility as a conserved, homologous, functional member of the disclosed protein families. Thus, this rejection is now moot. Moreover, this rejection as it applies to new claims 45-53, which claim a the polymorphic nucleotide sequence of SEQ ID NO: 509 or a complement thereof is also moot. Accordingly, Applicants request that this rejection be withdrawn.

Claims 1-18 are also rejected under 35 U.S.C. § 112, first paragraph for alleging that since the invention is not supported by either a specific or substantial asserted utility, one skilled in the art would not know how to use the claimed invention.

Applicants traverse. For the reasons set forth above, Applicants submit that the claimed invention has a specific and substantial or well-established utility. Therefore, this rejection is now moot as it applies to pending claims 1-6, 9, 10, 12, 14 and 45-53 and should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH

Claims 9 and 17 have been rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have cancelled claim 17 and claim 9 has been amended herein to recite that the elected polynucleotide of SEQ ID NO: 509 is comprised within a nucleic acid encoding a polypeptide homologous to a keratinocyte growth factor. The Examiner's position is that claim 9 does not satisfy the written description requirement because the claim is not limited to a nucleic acid encoding a human growth factor. As discussed *supra*, the nucleotide sequence of SEQ ID NO: 509 is a conserved nucleic acid sequence of the keratinocyte growth factor protein family (*see* specification, Table 1, column 11). Claim 9 has been amended to recite a polynucleotide comprised within a nucleic acid encoding a polypeptide homologous to a keratinocyte growth factor. Therefore, Applicants assert that claim 9 as amended herein meets the written description provision of 35 USC 112, first paragraph. Applicants request that this rejection be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 1-18 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts, at page 9 of the Office Action, that the recitation of non-elected SEQ ID NOs in parentheses in claims 1, 14 and 15 renders these claims indefinite. Applicants have cancelled claim 15 and amended claims 1 and 14 to delete parentheses and delete reference to the non-elected SEQ ID NOs. These amendments also relate to new claims 45-53 which do not recite non-elected SEQ ID NOs in parentheses. Pending claims 1-6, 9, 10, 12, 14 and 45-53 now recite the polymorphic nucleotide sequence of SEQ ID NO: 509. Applicants request this rejection be withdrawn.

The Examiner has also indicated that the recitation of a polynucleotide "derived from" a nucleic acid encoding a polypeptide "related to" a list of proteins renders claims 9 and 17 indefinite (Office Action at page 10). Applicants have cancelled claim 17 and claim 9 has been amended herein to recite that the elected polynucleotide of SEQ ID NO: 509 is comprised within a nucleic acid encoding a polypeptide homologous to a keratinocyte growth factor. As discussed

supra, the nucleotide sequence of SEQ ID NO: 509 is a conserved nucleic acid sequence of the keratinocyte growth factor protein family (*see* specification, Table 1, column 11). Applicants have also amended claim 9 to delete the phrase "related to" and recite the phrase "homologous to". Homology is readily determined by the skilled artisan using BLAST analysis or homology alignment algorithms as described in the specification (*See* specification, pg 26, lines 5-13; pg 36, line 23 – pg 37, line 6). Therefore, Applicants submit that claim 9 as amended herein is no longer indefinite. Applicants request that this rejection be withdrawn.

The Examiner has rejected claims 1, 14 and 15 as allegedly being indefinite for reciting the term "complementary nucleotide sequence" (Office Action at pages 10-11). Applicants have cancelled claim 15 and amended claims 1 and 14 to delete the phrase "complementary nucleotide sequence" Applicants request that this rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Dated: May 28, 2002

Version with Markings to Show Changes

In the Specification:

The priority information on page 1 was amended as follows:

-- This application is a continuation-in-part of U.S.S.N. 09/442,849, filed November 17, 1999, which claims priority to U.S.S.N. [USSN] 09/442,129 and U.S.S.N. [USSN] 09/443,199 [____], both filed November 16, 1999, [all of which are entitled "Nucleic Acids Containing Single Nucleotide Polymorphisms and Methods of Use Thereof" and naming Richard Shimkets and Martin Leach as inventors,] and to U.S.S.N. [USSN] 60/109,024, filed November 17, 1998. The contents of these applications are incorporated herein by reference in their entirety. --

The paragraph beginning at line 8 on page 23 was amended as follows:

-- The first column of the table lists the names assigned to the fragments in which the polymorphisms occur. The fragments are all human genomic fragments. The sequence of one allelic form of each of the fragments (arbitrarily referred to as the prototypical or reference form) has been previously published. These sequences are listed at the Whitehead Institute/MIT Center for Genome Research web site [http://www-genome.wi.mit.edu/] (all STS's sequence tag sites)); the Stanford Human Genome Center web site [http://shgc.stanford.edu] (Stanford STS's); and The Institute for Genomic Research web site [http://www.tigr.org/] (TIGR STS's). The web sites also list primers for amplification of the fragments, and the genomic location of the fragments. Some fragments arc expressed sequence tags, and some are random genomic fragments. All information in the web sites concerning the fragments listed in the table is incorporated by reference in its entirety for all purposes. --

In the Claims:

1. (Amended) An isolated polynucleotide comprising the polymorphic nucleotide sequence of SEQ ID NO: 509 [selected from the group consisting of:

a) a nucleotide sequence comprising one or more polymorphic sequences (SEQ ID NOS:1 - 651);

b) a fragment of said nucleotide sequence, provided that the fragment includes a polymorphic site in said polymorphic sequence;

c) a complementary nucleotide sequence comprising a sequence complementary to one or more of said polymorphic sequences (SEQ ID NOS:1 - 651); and

d) a fragment of said complementary nucleotide sequence, provided that the fragment includes a polymorphic site in said polymorphic sequence].

4. (Amended) The polynucleotide of claim 1, wherein said polynucleotide sequence is between about 10 and about 50 [100] nucleotides in length, and wherein at least 10 contiguous bases include the nucleotide corresponding to position 26 of SEQ ID NO: 509.

5. (Amended) The polynucleotide of claim 1, wherein said polynucleotide sequence is between about 10 and about 40 [90] nucleotides in length, and wherein at least 10 contiguous bases include the nucleotide corresponding to position 26 of SEQ ID NO: 509.

6. (Amended) The polynucleotide of claim 1, wherein said polynucleotide sequence is between about 10 and about 30 [75] nucleotides in length, and wherein at least 10 contiguous bases include the nucleotide corresponding to position 26 of SEQ ID NO: 509.

9. (Amended) The polynucleotide of claim 1, wherein said polynucleotide is comprised within [derived from] a nucleic acid encoding a polypeptide homologous [related] to a keratinocyte growth factor [angiopoietin, 4-hydroxybutyrate dehydrogenase, ATP-

dependent RNA helicase, MHC Class I histocompatibility antigen, or phosphoglycerate kinase].

10. (Amended) The polynucleotide of claim 1, wherein a [said] polymorphic site includes any [a] nucleotide other than the nucleotide listed in Table 1, column 5 for said polymorphic sequence.

12. (Amended) The polynucleotide of claim 1, wherein a [said] polymorphic site includes the nucleotide listed in Table 1, column 6 for said polymorphic sequence.

14. (Amended) An isolated allele-specific oligonucleotide that hybridizes to a first polynucleotide at a polymorphic site encompassed therein, wherein the first polynucleotide comprises the polymorphic nucleotide sequence of SEQ ID NO: 509 [is chosen from the group consisting of:

a) a nucleotide sequence comprising one or more polymorphic sequences (SEQ ID NOS:1 - 651) provided that the polymorphic sequence includes a nucleotide other than the nucleotide recited in Table 1, column 5 for said polymorphic sequence;

b) a nucleotide sequence that is a fragment of said polymorphic sequence, provided that the fragment includes a polymorphic site in said polymorphic sequence;

c) a complementary nucleotide sequence comprising a sequence complementary to one or more polymorphic sequences (SEQ ID NOS:1 - 651), provided that the complementary nucleotide sequence includes a nucleotide other than the complement of the nucleotide recited in Table 1, column 5; and

d) a nucleotide sequence that is a fragment of said complementary sequence, provided that the fragment includes a polymorphic site in said polymorphic sequence].

-- 45. (New) The oligonucleotide of claim 14, wherein the oligonucleotide which hybridizes to the polynucleotide comprising the polymorphic nucleotide sequence of SEQ ID NO: 509 identifies a nucleic acid encoding a polypeptide homologous to a keratinocyte growth factor.

46. (New) An isolated polynucleotide comprising a sequence complementary to the polymorphic nucleotide sequence of SEQ ID NO: 509.

47. (New) The polynucleotide of claim 46, wherein said polynucleotide sequence is DNA.

48. (New) The polynucleotide of claim 46, wherein said polynucleotide sequence is RNA.

49. (New) The polynucleotide of claim 46, wherein said polynucleotide is between about 10 and about 50 bases in length.

50. (New) The polynucleotide of claim 46, wherein said polynucleotide is between about 10 and about 40 bases in length.

51. (New) The polynucleotide of claim 46, wherein said polynucleotide is between about 10 and about 30 bases in length.

52. (New) The polynucleotide of claim 46, wherein the complement of a polymorphic site includes the complement of any nucleotide other than the nucleotide listed in Table 1, column 5 for said complementary polymorphic nucleotide sequence.

53. (New) The polynucleotide of claim 46, wherein the complement of a polymorphic site includes the complement of the nucleotide listed in Table 1, column 6 for said complementary polymorphic nucleotide sequence. --